Conjunctive and Disjunctive Eye Movements an Pupillary Response Performance for Objective Metrics in Acute mTBI

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Disclosures

- Michael E. Hoffer and Carey D. Balaban have no conflicts of interest or financial interests to report
- Alexander Kiderman is an employee and shareholder of Neuro Kinetics, Inc.
- The views expressed in this talk are those of the author(s) and do not necessarily reflect the official policy or position of the University of Pittsburgh, University of Miami, Department of the Navy, Department of Defense, or the U.S. Government.

Why is mTBI a Topic for Otolaryngology?

- Balance disorders often present
- Co-morbidities similar to balance-migraine-anxiety
- Vestibular, oculomotor and reaction time tests provide objective metrics for acute mTBI

Precision Medicine

- **Current clinical nosology as a clinical descriptive template**
  - **Symptoms**
  - **Signs**
  - **“Biomarkers”**
- **Establish etiologic nosology**
  - **Identify acute response processes**
  - **Identify longitudinal processes**
  - **Plan interventions appropriate to patients’ clinical trajectories**

‘Plain Language’ mTBI Definition

- **Documented traumatic event**
- **‘Not Quite Right’ (‘NQR’ criterion)**
- **How does one quantify ‘NQR’?**

Conjunctive Eye Movements as Objective mTBI Metrics: Up to 2 Weeks Post-Injury

PLOS ONE

RESEARCH ARTICLE

Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury

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Laryngoscope Investigative Otolaryngology

The Use of Oculomotor, Vestibular, and Reaction Time Tests to Assess Mild Traumatic Brain Injury (mTBI) Over Time

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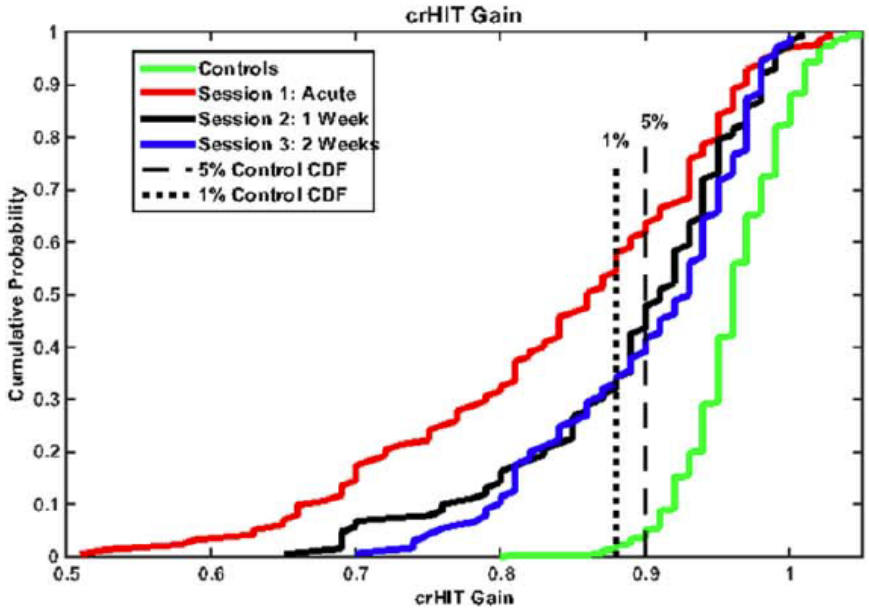
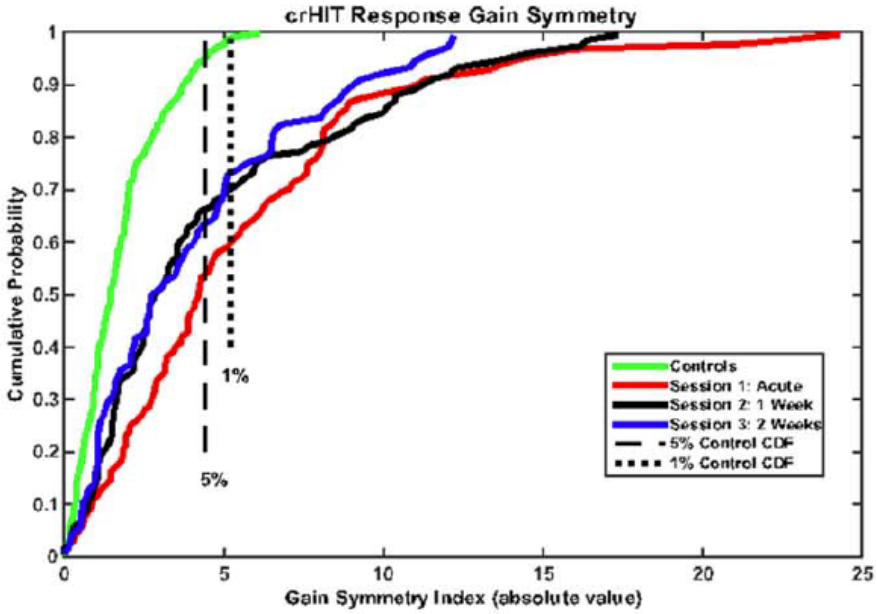
Conjuctive (Conjugate) Eye Movements for mTBI Diagnosis

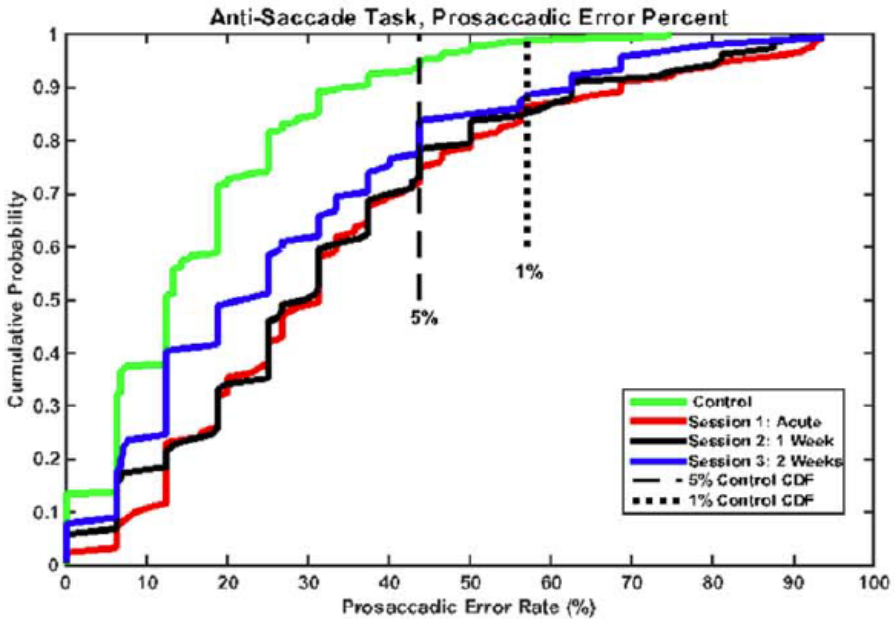
- High Frequency Horizontal Vestibulo-ocular Reflex
  - Computer-controlled Head Impulse Test (crHIT)
- Saccades
  - Antisaccade Task
  - Predictive Saccade Task
- Optokinetic Response
- Smooth Pursuit

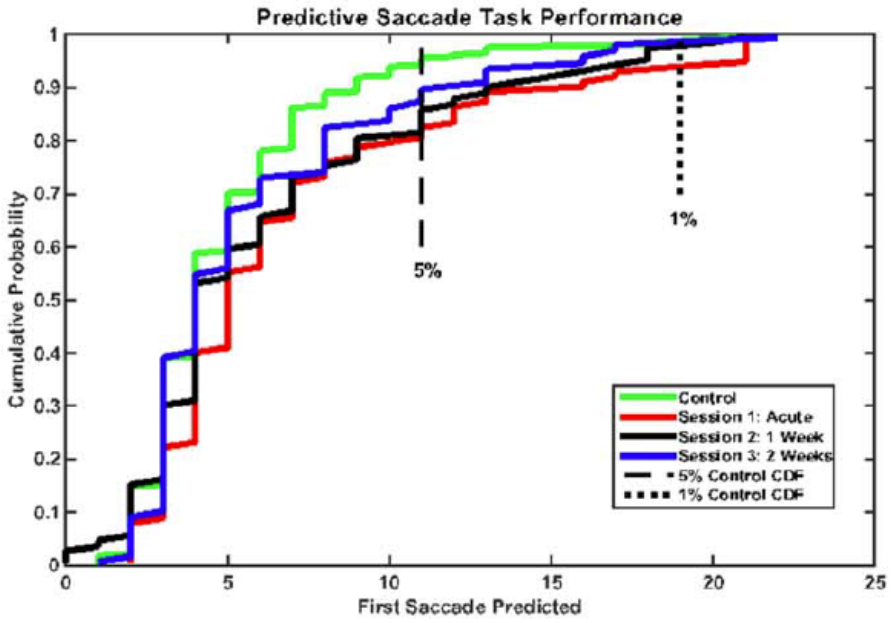
Key Measure Changes Across Sessions





Key Measure Changes Across Sessions





Background

- Disconjugate eye movements (convergence and divergence) track objects that vary in depth over the binocular visual field. These eye movements can be measured objectively and are commonly affected following mTBI.

- Convergence insufficiency, determined by static measures of vergence function, has been associated with mTBI
  - Receded near point of convergence amplitude
  - Decreased compensatory fusional ranges at near distances
  - Abnormal phoria at near or far displacements (horizontal, vertical)

Vergence Eye Movements in TBI

- Thiagarajan P, Cuiffreda KJ, Ludlam DP. Vergence dysfunction in mild traumatic brain injury (mTBI): a review. Ophthalmic Physiol Opt 2011, 31: 456-468.
- Alvarez TL, Kim ET, Vicci VR, Dhar SK, Biswal BB, Barrett AM. Concurrent visual dysfunctions in convergence insufficiency with traumatic brain injury. Optom Vis Sci 2012, 89:1740-1751
- Tyler CW, Likova LT, Mineff KN, Elsaid AM, Nicholas SC. Consequences of traumatic brain injury for human vergence dynamics. Front Neurol 2015, 5:282

Vergence and the Near Triad

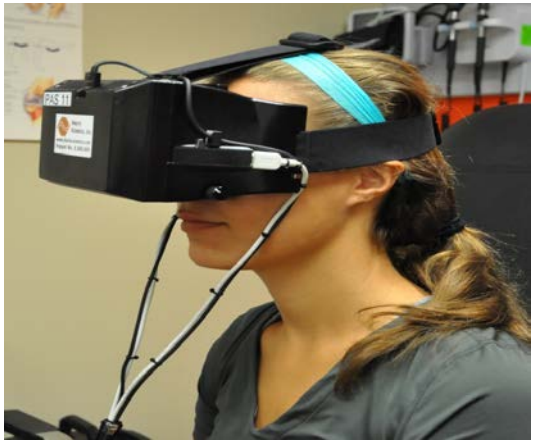
- Coordinated movements of eyes, pupil and lens
  - Convergence
  - Pupil constriction (miosis)
  - Lens accommodation

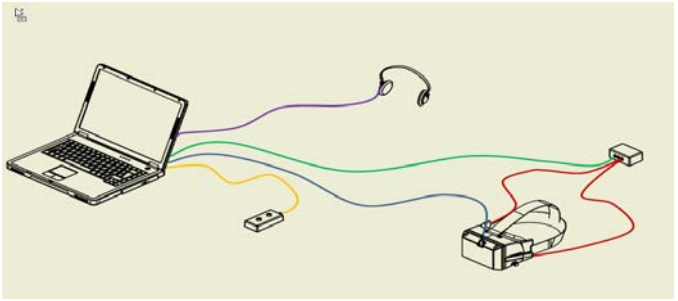
Vergence and Pupil Movement in mTBI

- Examined virtual vergence task in control subjects and patients with acute mTBI
- Examined
  - Convergence eye movements
  - Pupil area
  - Coordination between convergence eye movements and pupil area changes

Hardware and Software

- Conducted with the I-PAS™ (I-Portal® Portable Assessment System, NKI Pittsburgh), a portable 3D head mounted display (HMD) system with integrated eye tracking technology.
  - Sampling rate 100 Hz
  - Resolution < 0.1°
- All stimuli were created in a virtual environment.
- Neuro Kinetics VEST™ software was used to run the battery of tests and analyze the data.





Virtual Vergence Tracking Task

- Monocular targets do not change in size or brightness
  - White square with red center ~0.1 degrees visual angle for each eye
  - Total field luminance: 0.05-0.06 cd/ m ^{2}
- Move toward and away from midline
- Produce ± 2.6 deg of convergence and divergence

Virtual Vergence Tracking Task

- Dependent variables:
  - Vergence angle re: zero at resting tropia (calibration)
  - Pupil area
    - Normalized to response range of pupillary light response:
      - Monocular 5° visual angle disc
      - Uniform illumination at intensity range 0.42 to 65.4 cd/m ^{2}
      - Expressed as percent of response range (0-100 scale)

Control Subjects

- 36 male (69.2%), 16 female (30.8%)
  - Mean: 28.7 years
  - Range: 21 to 45 years
  - SD: 6.3 years

mTBI subjects

- 13 male (76.5%), 4 female (23.5%)
  - Mean: 29.1 years
  - Range: 20 to 43 years
  - SD: 8.1 years

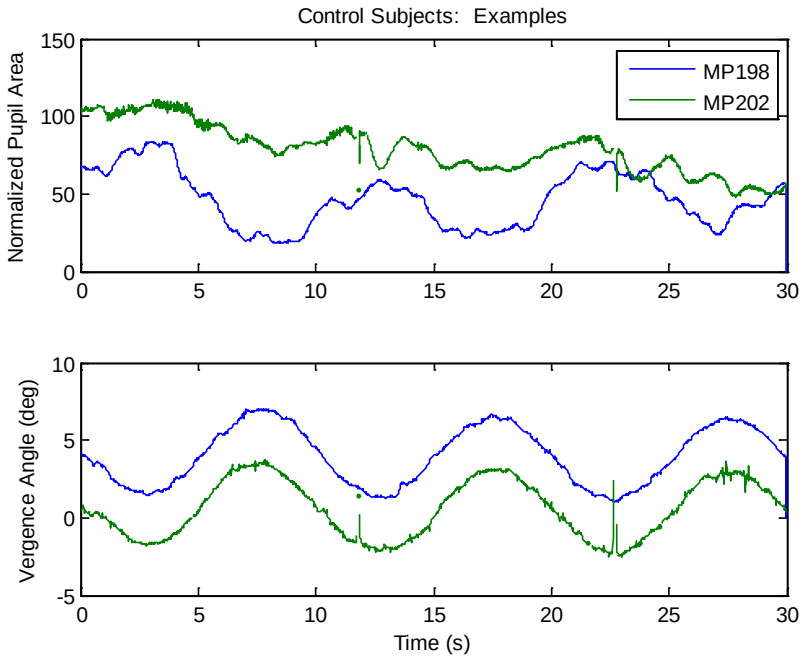
Study Design

- mTBI subjects and controls were tested at three sites:
  - University of Miami Miller School of Medicine
  - Madigan Army Medical Center
  - Naval Medical Center San Diego
- All mTBI subjects were diagnosed by an emergency room physician
- mTBI subjects tested using the following time line

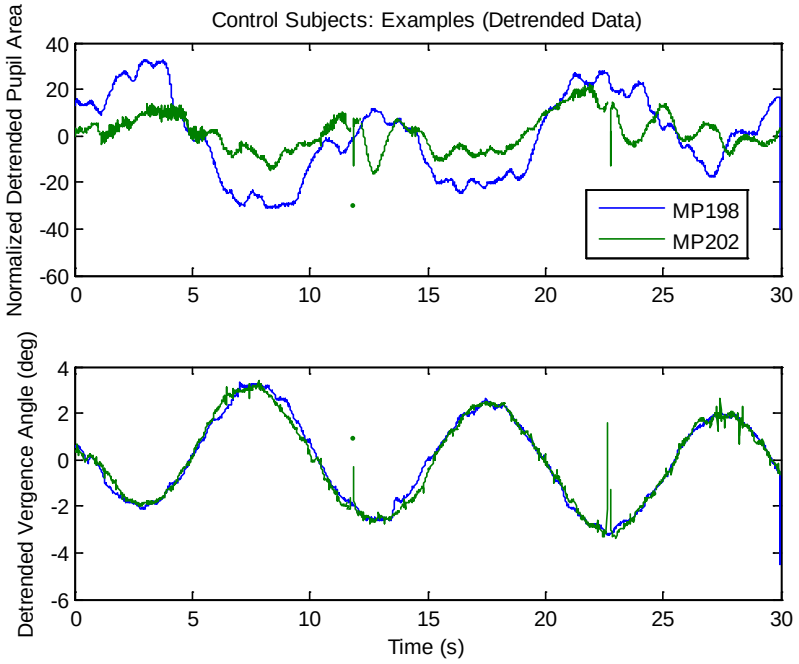
Data Analysis

- Pupillary light test used to normalize pupil area
- Vergence angle represented in degrees relative to zero at initial fixation

Control Subjects: Variability Examples (Raw Data)



Control Subjects: Variability Examples (Detrended Data)

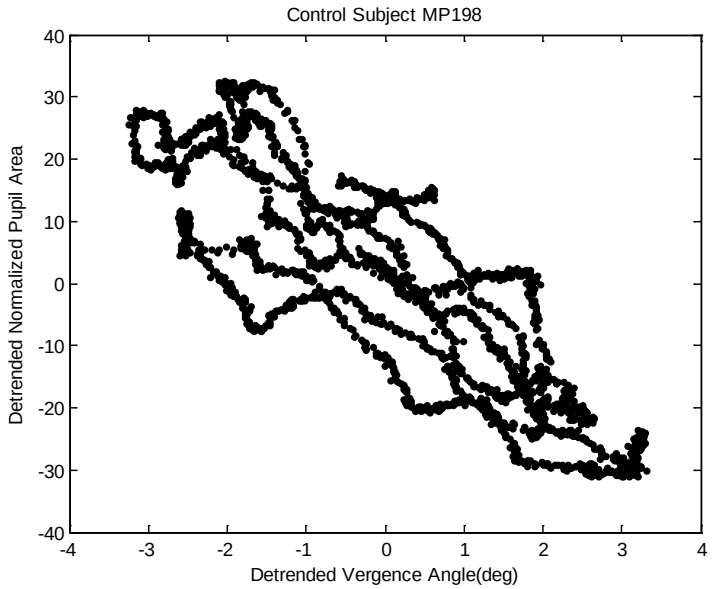


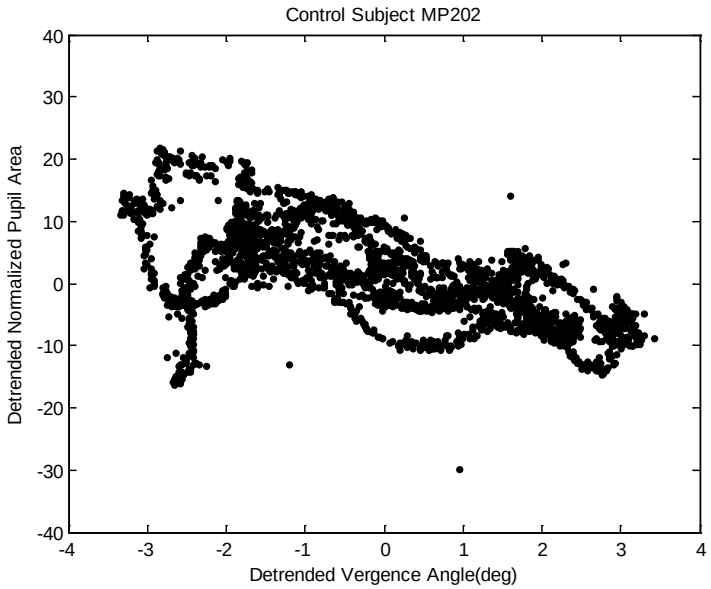
Half-Cycle Gains for Eye Movement and Pupil Components at 0.1 Hz

Session	N	Component	Direction	Magnitude (±SE)	R^2 (±SE)
Control	52	Vergence	Toward	2.537 ± 0.110°	0.933 ± 0.088
			Away	2.258 ± 0.100°	
		Pupil	Toward	23.538 ± 1.574%	0.563 ± 0.198
			Away	13.428 ± 1.955%	
		Vergence-Pupil Phase		2.93 ± 0.04 rad	

Model: Least squares estimate of linear trend plus half cycle gains (toward and away)

Control Subjects: Variability Examples (Detrended Vergence-Pupil Coordination)

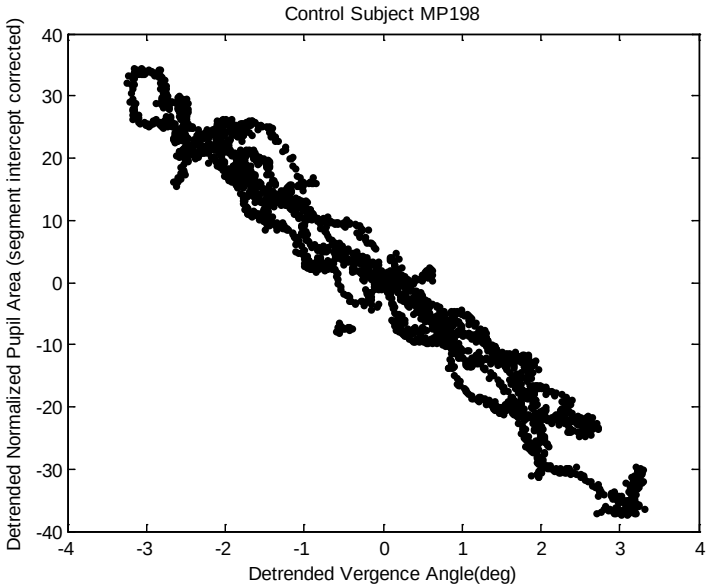




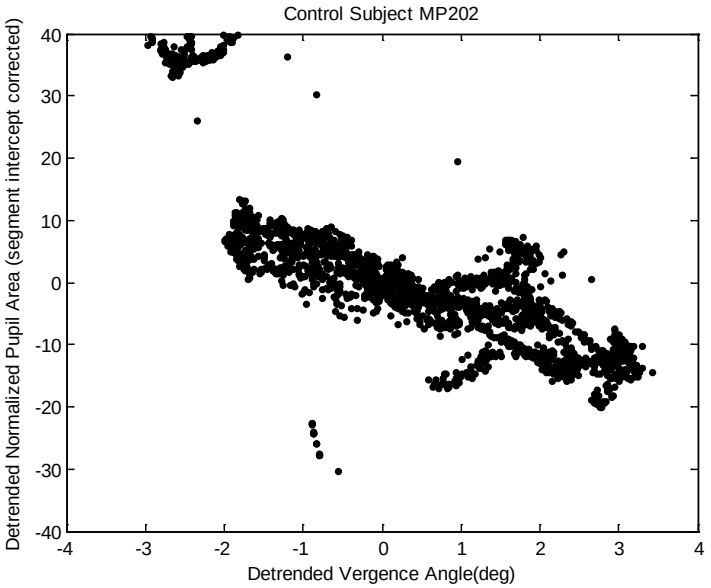
Piecewise Linear Analysis of Eye and Pupil Movement Coordination

- The sampled detrended normalized pupil area and detrended vergence angles are a multivariate time series
- A modified Gath-Geva clustering algorithm (Abonyi et al. Fuzzy Sets and Systems 149:39–56, 2005) was used for objective fuzzy segmentation of the time series into 15 segments with homogeneous properties.
  - Clustering algorithm for simultaneous identification of local probabilistic principal component analysis models
  - Based upon measured homogeneity of the segments and fuzzy sets used to represent the segments in time.
  - One principal component selected (represents the association between eye and pupil movements)

Plots After Subtraction of Linear Segment Intercept

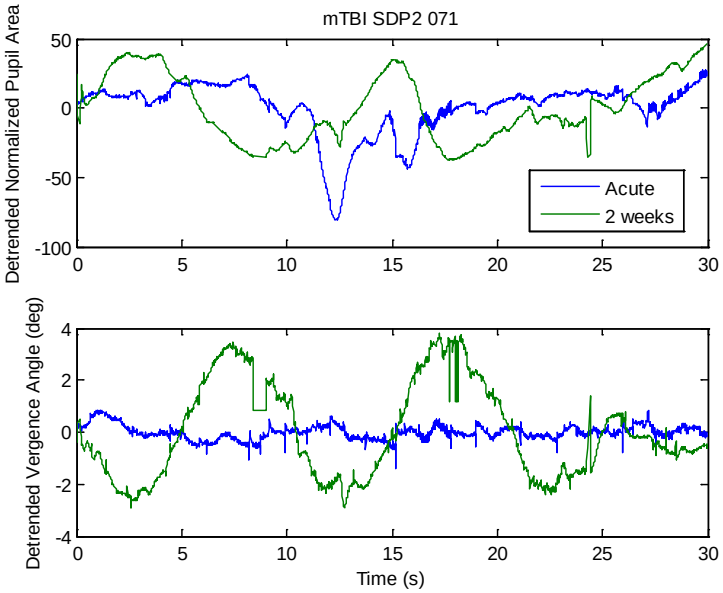


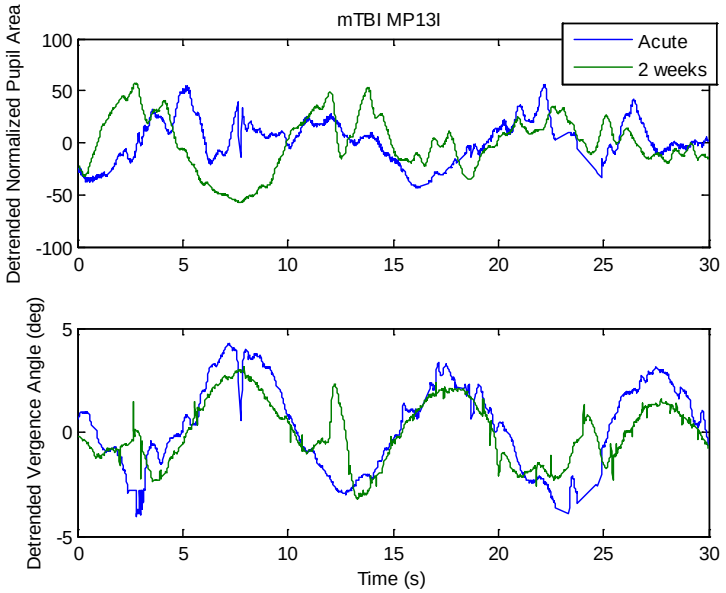
R^2=0.948



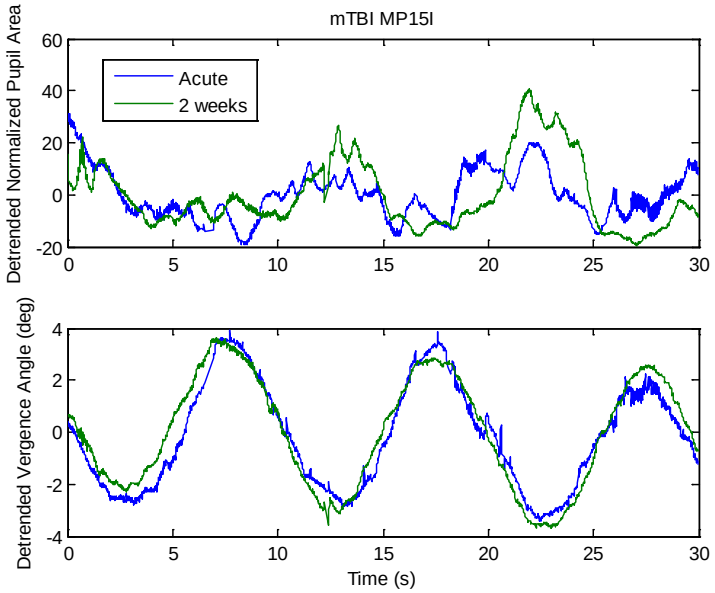
R^2=0.663

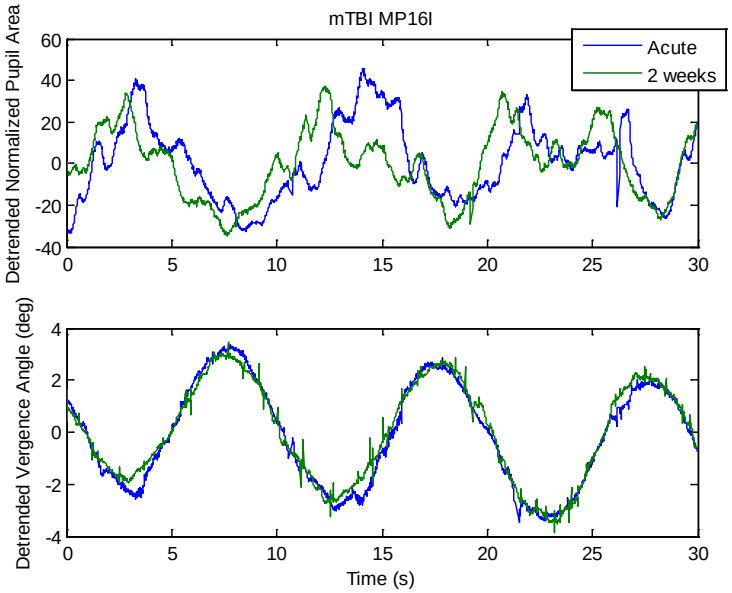
mTBI Subjects: Variability Examples (Detrended Data)





mTBI Subjects: Variability Examples (Detrended Data)





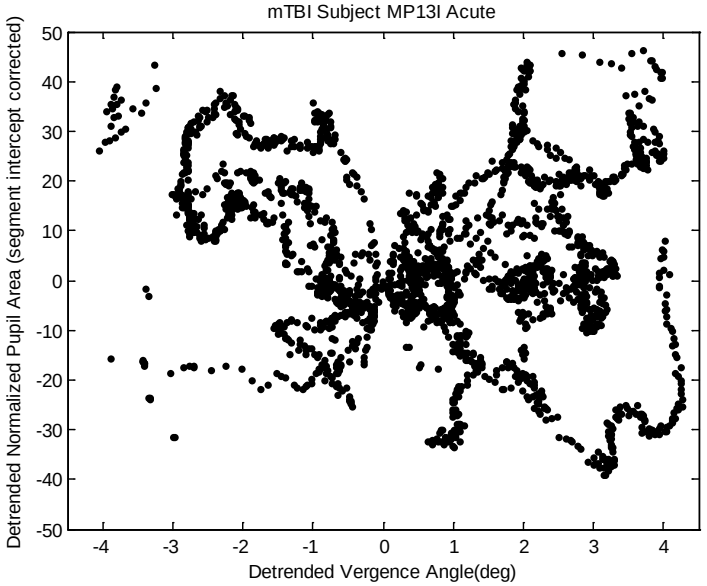
Eye Movements and Pupil Movements

(half cycle parameter estimates by LS regression)

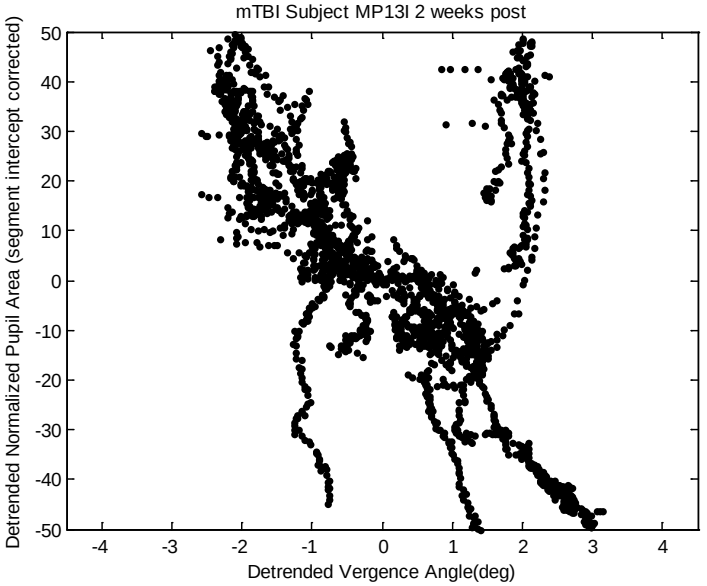
Session	N	Component	Direction	Magnitude (±SE)	R^2 (±SE)
Control	52	Vergence angle	Toward	2.54 ± 0.11°	0.933 ± 0.088
			Away	2.26 ± 0.10°	
		Pupil area	***Toward***	***23.54 ± 1.57%***	***0.563 ± 0.198***
			Away	***13.43 ± 1.96%***	
		Vergence-Pupil Phase		**2.93 ± 0.04 rad**	
Acute	17	Vergence angle	Toward	**1.75 ± 0.19°**	**0.652 ± 0.316**
			Away	1.864 ± 0.18°	
		Pupil area	***Toward***	***14.71 ± 2.75%***	***0.378 ± 0.247***
			Away	***7.80 ± 3.42%***	
		Vergence-Pupil Phase		**2.49 ± 0.08 rad**	
Subacute (2w)	14	Vergence angle	Toward	2.63 ± 0.21 °	0.931 ± 0.101
			Away	2.34 ± 0.19°	
		Pupil area	Toward	17.52 ± 3.03%	0.528 ± 0.235
			Away	12.50 ± 3.77%	
		Vergence-Pupil Phase		**2.69 ± 0.08 rad**	

Red denotes significantly different from Control by Tukey HSD tests

Plots After Subtraction of Linear Segment Intercept: mTBI example



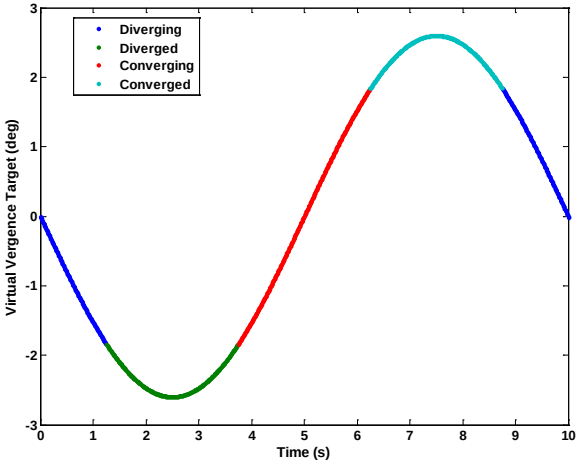
R^2=0.195



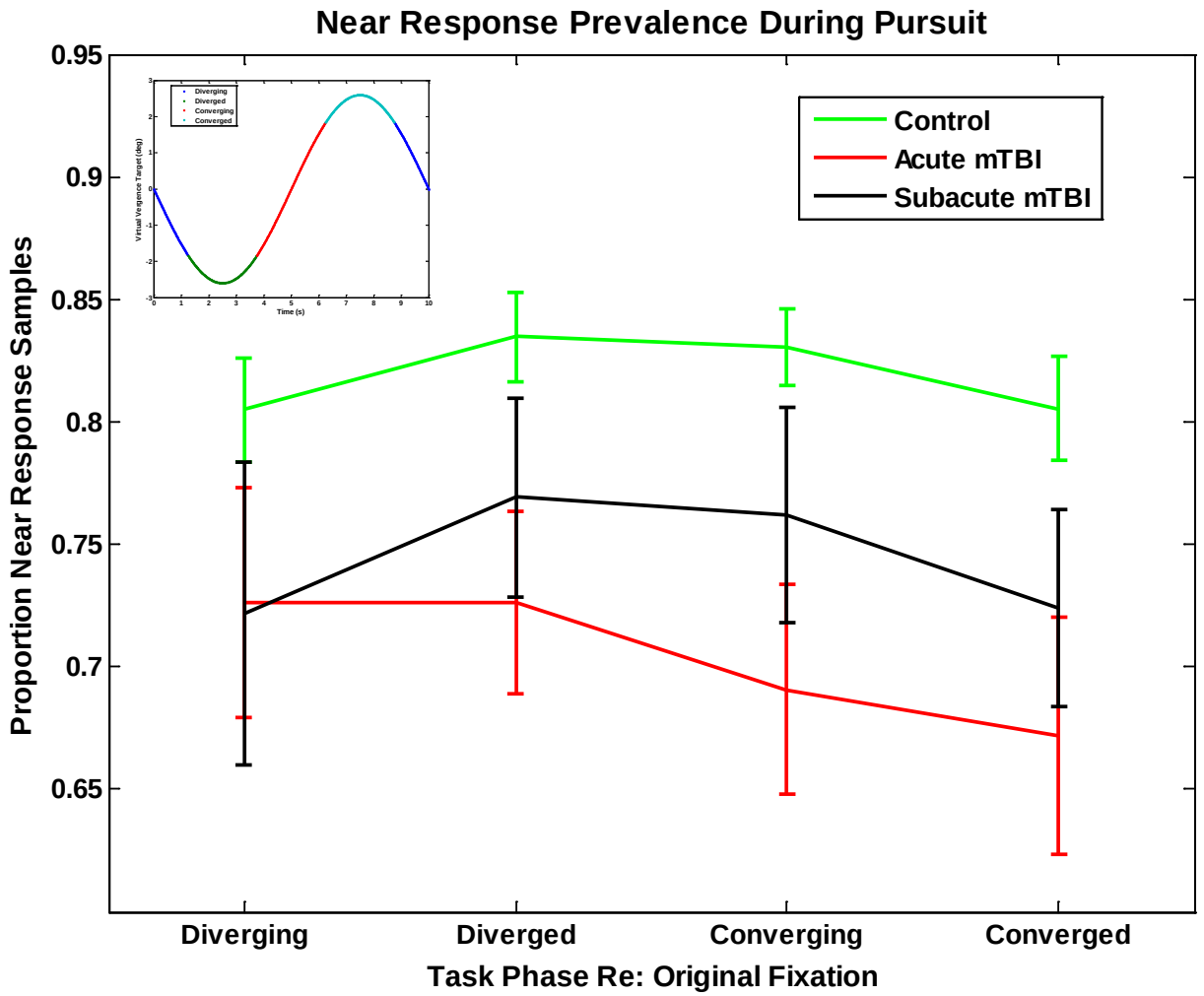
R^2= 0.275

Eye Movements and Pupil Movements in mTBI

- Calculated the proportion of the time in a near response relationship (i.e., pupil constricts in convergence and dilates during divergence) in each of four conditions:
  - Eyes diverging
  - Eyes diverged
  - Eyes converging
  - Eyes converged



Eye Movements and Pupil Movements in mTBI



Logistic Regression for Acute versus Control (Only Vergence Pursuit Data)

Observed Group	Control (Predicted)	mTBI (Predicted)	Percent Correct
Control	50	2	96.2%
mTBI acute	4	13	76.5%
Overall Percentage			92.2%

	B	SE	Wald	df	Signif	Exp(B)
R^2 for Vergence Sinusioidal Fit	-9.844	3. 711	7.038	1	0.008	0.000
Vergence-Pupil Phase Difference	-5.773	1.988	8.435	1	0.004	0.003
Vergence Modulation Diverging	1.860	0.821	5.135	1	0.023	6.425
Pupil Modulation Dilating	-0.057	0.034	2.744	1	0.098	0.945
Constant	19.676	5.416	13.198	1	0.000	350937889.400

Logistic Regression for Session 1 versus Control (All)

Observed Group	Control (Predicted)	mTBI (Predicted)	Percent Correct
Control	45	2	95.7%
mTBI acute	3	14	82.4%
Overall Percentage			92.2%

	B	SE	Wald	df	Signif	Exp(B)
Vergence Fit R squared	-16.669	7.325	5.179	1	0.023	0.000
Vergence-Pupil Phase Difference	-5.998	2.365	6.429	1	0.011	0.002
First Predictive Saccade	0.240	0.105	5.255	1	0.022	1.271
Absolute Subjective Visual Vertical	0.918	0.418	4.824	1	0.028	2.504
Constant	26.714	7.799	11.733	1	0.001	399576846217

Conclusions

- In acute mTBI, a majority of patients showed
  - Depressed modulation magnitude and increased variability for ocular convergence (smooth pursuit)
  - Depressed modulation magnitude and increased variability of pupil constriction during convergence
  - Diminished coordination between the ocular convergence and pupil responses
- The performance showed recovery within 2 weeks in this small cohort of 17 mTBI subjects

Summary

- Tests involving both motor performance and cognitive function can objectively identify patients with a diagnosis of acute mTBI
- Test metrics can be used for follow-up
- Metrics selected empirically—require ‘sense-making’ in terms of mechanisms of injury and recovery

Summary

- Challenge: When are patients ready to return to normal activities (no longer ‘NQR’)?

From the Battlefield to the Brickyard